REMARKS

Claims 1-9, 11-20 and 25-37 were pending in the subject application. By this Amendment applicants have canceled claim 33 without prejudice and have amended the claims as indicated above. Accordingly, claims 1-9, 11-20, 25-32 and 34-37 are pending in the subject application.

The Examiner has objected to Claim 33 under 37 CFR 1.75(c).

In response, claim 33 has been cancelled without prejudice.

The Examiner has objected to Claims 1-9, 11-20, 23 and 25-37 under 35 U.S.C. 112, second paragraph.

In response, claims 1, 13, 14, 16, 17, 23, 31, 32, 35, 36 and 37 have been amended to better define the invention. Favourable reconsideration and allowance of the subject application are respectfully requested in view of the amendments and the following comments.

The phrase "the or each discontinuous phase" in Claims 1 and 23 has been amended to read "the at least one discontinuous phase".

A comma has been inserted in Claim 13 to better define that the phrase "or an ester thereof" is intended to refer to every member of the Markush group recited therein.

Claims 14, 32, 36 and 37 have been amended to remove the phrase ", said carrier comprising water as the continuous phase".

Claim 16 has been amended to better define the invention. More specifically, the phrase "or a mixture thereof" has been amended to read ", and a mixture thereof" to better define that this phrase is intended to refer to every member of the Markush group recited therein. The phrases "modified celluloses" and "modified starches" have been deleted from Claim 16 without prejudice. Claim 16, as now presented, is intended to refer to a Markush list of five alternatives (carbomers; naturally occurring synthetic or semi-synthetic gums; co-polymers formed between maleic anhydride and methyl vinyl ether; colloidal silica; methacrylates) or a mixture.

Claim 17 has been amended to better define the invention and as suggested by the Examiner. No new matter has been added.

The amendments suggested by the Examiner in relation to Claim 23 have been followed.

The Examiner has objected to the term "consists". This has been replaced in claims 31 and 35 by the term "is".

Claims 1-9, 11-20, 23, 25-29 and 31-37 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Francois et al.

In response, applicant notes that claims 1-9, 11-20, 25-29 and 31-32 of the instant invention are directed to an emulsion composition having a eutectic mixture of at least two active agents in at least one of the discontinuous phases. The basis of the Examiner's primary argument is that the Francois et al. compositions, in <u>separately</u> containing chlorocresol, ketoconazole and possibly stearyl alcohol, are the same as

applicants' compositions, which contain, in a eutectic mixture, chlorocresol, ketoconazole and possibly stearyl alcohol.

However, applicants point out that the mere separate presence of two or three eutectic-forming components does not, of itself, demonstrate the presence of a eutectic mixture of those two or three eutectic-forming components. Simply stated, eutectic-forming components do not necessarily form a eutectic mixture.

Specifically, page 1, line 15 of the instant specification teaches that a eutectic mixture of two eutectic-forming solids will only occur
"upon intimate admixture of the two solids (emphasis added)*"*
Page 1, lines 17-19 of the instant specification teaches that this required intimate admixture of two solids usually, but not always, requires melting the two eutectic-forming components together.

Thus, a composition may contain two or more components, which are capable of forming a eutectic mixture, but a eutectic mixture may not actually be present.

For example, at page 14 of the instant specification, Formulations A and B each contain ibuprofen and methyl nicotinate and are identical in composition except that, in Formulation B, the emulsifying agent is omitted. Under these circumstances, Formulation B is disclosed as being *"merely a physical mixture of two pharmacologically active agents, the eutectic mixture not being maintained in the absence of a*

stabilizing emulsifier."

Similarly, pages 15-16 of the instant specification teach a general method for preparing the eutectic compositions of Examples 2-6, whilst the text at pages 16-17 teaches how to prepare non-eutectic comparative compositions, in which the first and second active agents are merely in physical admixture. Such comparative non-eutectic compositions are prepared by providing a gelled aqueous phase to which the first and second active agents are sequentially added. Thus, the non-eutectic compositions are prepared by <u>avoiding</u> intimate admixture. Stated otherwise, the sequential addition of the comparative examples, *"serve(s) to reduce intimate contact between the eutectic-forming components"*.

Thus, the instant specification teaches that, if a eutectic mixture is sought, then specific process conditions must be met, namely, to cause the eutectic-forming components to come into, and maintain, intimate contact with each other. In other words, one skilled in the art must <u>intend</u> to form a eutectic mixture, and must affirmatively modify the process conditions accordingly.

Page 2, lines 3-19 of the instant specification teaches that, in the pharmaceutical field, the formation of a eutectic mixture is *"often regarded as problematic and undesirable."* For this reason, a man of ordinary skill in the art would be inclined to <u>avoid</u> any process conditions that would allow a eutectic mixture to form. If he were aware that two components were capable of forming a eutectic mixture, he would actively avoid their intimate admixture.

Page 4, lines 20-24 of the instant specification teaches that one of ordinary skill in the art would be discouraged from mixing two active agents *"due to the increased possibility of adverse physical and/or chemical interactions between the active drugs."*

For this reason, also, one of ordinary skill in the art would be inclined to avoid any process conditions that would bring two or more active agents into direct mixture with each other.

For both of the described reasons, applicants submit there is a strong prejudice leading one of skill in the art to avoid directly mixing two active agents.

Applicants note that Francois et al. teach emulsions, in which ketoconazole is suspended, for topical application to the skin. Applicants also note that Francois et al. teach that oil-in-water emulsions are preferred, and that Francois et al. teach that a preservative such as chlorocresol or an oil phase constituent such as stearyl alcohol may be included in the Francois et al. emulsions. However, applicants contend that there is no eutectic mixture of at least first and second actives actually present in the Francois et al. emulsion compositions.

The problem faced by Francois et al. is to provide a ketoconazole-containing emulsion, without significant degradation of the ketoconazole, but avoiding the use of sodium sulfite. Francois et al., therefore, teaches that ketoconazole is subject to degradation by oxidation. Dissolved ketoconazole is more subject to degradation than solid ketoconazole. The problem is solved by suspending the

ketoconazole in water (i.e. keeping it out of solution) and by maintaining the formulation's pH within a strict range (see column 1, lines 25-28). Thus, the type I creams are adjusted to pH 6-8 after the water/oil/water phases are mixed and the type II emulsion gels are adjusted to pH 6-8 before the ketoconazole is suspended therein.

In Francois et al., the creams of type I are prepared by dissolving the preservatives and wetting agents in water, into which the ketoconazole is then suspended. Similarly, Example 2 of Francois et al. is a cream of type I, in which two preservatives - diazolidinyl urea and sodium EDTA - are dissolved in water, into which the ketoconazole microfine is suspended. In other words, in the type I creams, the ketoconazole is suspended in water. Unless the suspended or solid ketoconazole subsequently migrates to the oil phase, which is unlikely, the ketoconazole is not present in the oil phase. In addition, the preservatives are dissolved in water. Again, unless the preservatives subsequently migrate to the oil phase, which is unlikely, the preservatives are not present in the oily phase. Even if the ketoconazole and the preservatives both subsequently migrate to the oil phase in Francois et al., as unlikely as that is, the method of preparing the type I creams, in which the preservatives and the ketoconazole are separately added to a water phase, means that a eutectic mixture of ketoconazole and a eutectic-forming preservative cannot form.

In Francois et al, the emulsion gels of type II are prepared by dissolving the preservatives in water; forming an emulsion; and then suspending the ketoconazole in the emulsion. Similarly, Example 1 is an emulsion gel of type II, in which

two preservatives - cetrimide and sodium EDTA - are dissolved in water, following which an emulsion gel is formed, into which the ketoconazole microfine is suspended. In other words, in the type II emulsions, the ketoconazole is suspended in the emulsion, with the preservatives dissolved in the water. Unless the solid or suspended ketoconazole subsequently migrates to the oil phase, which is unlikely, the ketoconazole is not present in the oil phase. In addition, the preservatives, as already stated, are dissolved in water. Again, unless the preservatives subsequently migrate to the oil phase, which is unlikely, the preservatives are not present in the oily phase. Even if both the ketoconazole and the preservatives both subsequently migrate to the oily phase, the method of preparing the type II emulsions, in which the preservatives are dissolved in a water phase and the ketoconazole is subsequently added to the emulsion as a whole, means that a eutectic mixture of ketoconazole and a eutectic-forming preservative cannot form.

The Examiner acknowledged that Francois et al. do not exemplify a chlorocresol-containing composition. The Examiner also acknowledged that Francois et al. do not teach that its active agents are actually present in the discontinuous phase. Despite this, the Examiner alleged that ketoconazole is somehow present in the oily phase. Applicants contend that this assumption by the Examiner is unsupported by Francois et al. The preservatives described by Francois et al. at column 3, lines 27-47 are mainly non-eutectic forming components. There is no incentive to one skilled in the art to select chlorocresol from this long list - chlorocresol is neither a preferred preservative nor an exemplified preservative. In fact, there is a disincentive against selection of a eutectic-

forming preservative - it introduces a risk that the ketoconazole might dissolve more readily and, therefore, be more vulnerable to oxidation. This runs contrary to the entire teaching of Francois et al., whose invention concerns protecting ketoconazole from oxidative degradation, at least in part by suspending the ketoconazole in the aqueous phase.

Francois et al. teach in column 2, lines 6-8, that "*Up to 99% or more of the ketoconazole may be in suspension…, the remainder (if any) being dissolved.*" (emphasis added)

In each of the type I and II emulsions of Francois et al., the ketoconazole is suspended, rather than dissolved (see column 5, lines 38 and 54; column 6, lines 29 and 57). The ketoconazole is suspended in an aqueous phase (type I creams) and in an oil/water emulsion as a whole (type II emulsion gels).

In each of the type I and II emulsions of Francois et al., the preservatives are dissolved in water, rather than directly contacted with the ketoconazole. The Francois et al. process conditions for both the type I and II emulsions do not permit direct contact between preservatives and ketoconazole and, without that direct contact, a eutectic mixture of a ketoconazole and a eutectic-forming preservative such as chlorocresol will not occur.

In summary the compositions disclosed by Applicant and Francois et al. are fundamentally different because, in all cases, the compositions of Francois et al. have the solid drug suspended in the aqueous phase, and a separate oily phase.

The active pharmacological agent, ketoconazole, is a relatively high melting crystalline solid. In the compositions of Francois et al., the ketoconazole is present as a suspension in the aqueous phase of the emulsion. There is no suggestion that the ketoconazole, which is separately added, is forming a eutectic mixture with any of the major components of the compositions disclosed by Francois et al. and, indeed, it is readily apparent from basic physical chemistry that it is impossible for such an event to occur, given the disclosed process conditions. In summary, therefore, the aqueous phase of the emulsions in Francois et al. comprise an aqueous suspension of ketoconazole, in which a preservative has been prior-dissolved. There is no disclosure or suggestion that any preservative is present in the oily phase. There is no disclosure or suggestion that the ketoconazole is present in the oily phase. There is no disclosure or suggestion that a eutectic mixture is present.

The Examiner has also rejected the method claims (Claims 23 and 34-37) on the basis that any properties exhibited by, or benefits provided by, the compositions are inherent and are not given patentable weight over the prior art, i.e. a chemical composition and its properties are inseparable. The Examiner pointed out that the burden of proof is shifted in these circumstances to the Applicant. The Examiner, thus, requested Applicant to show that applying the prior art (Francois et al.) compositions to the skin does not inherently mutually enhance the dermal permeation of the two active agents, as is instantly claimed.

In response, applicants respectfully direct the Examiner's attention to the various topical compositions exemplified in

the instant specification, for example, Formulation A, which contains a eutectic mixture of ibuprofen and methyl nicotinate and Formulation B, which contains a non-eutectic mixture of ibuprofen and methyl nicotinate. Figures 3a and 3b of the instant specification illustrate that Formulation A, which does contain a eutectic mixture, shows dramatically improved penetration of both actives, when compared to Formulation B, which does not contain a eutectic mixture.

Applicants also direct the Examiner's attention to Examples 2-6, each of which exemplify a topical composition containing two actives, either in a eutectic mixture or not (the latter is described as a physical mixture). Thus, Figures 4a and 4b of the instant specification illustrate that the composition containing a eutectic mixture shows dramatically improved release of both actives, when compared to the comparative composition, in which both actives are merely in physical admixture. Similar comments apply having regard to Figures 5a and 5b; 6a and 6b; 7a and 7b; and 8a and 8b. Thus the instant compositions have been exemplified to have clear and unexpected advantages over formulations containing the same actives which do not possess the eutectic system within an oil phase of an emulsion.

Applicants therefore respectfully submit that the basis for the Examiner's rejection of all of the pending claims, which is founded upon an alleged identity with the respective compositions, is unfounded. There is a fundamental difference between the respective formulations of Applicant and Francois et al. and this difference is responsible for the unexpected advantages obtained with the instant compositions. The compositions of Francois et al., due to the absence of a

eutectic mixture in the oily phase, could not therefore be expected to exhibit the same advantageous properties as the instant compositions, i.e. exhibit mutually enhanced penetration characteristics of the pharmacologically active components.

Claim 30 has been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Francois et al as applied to Claims 1-9, 11-20, 23, 25-29 and 31-37 above and further in view of Becker et al (2002/0131983).

Given the above argument with respect to the fundamental differences between the compositions disclosed by Francois et al., and those described and claimed by Applicant, applicants respectfully submit that the additional objections raised by the Examiner with respect to xanthan gum as a gelling or suspension agent of the instant compositions are moot. The gelling or suspension agents of instant Claim 30 are stated to be disclosed by Becker et al. However, applicants submit that the use of xanthan gum as a gelling or suspension agent is patentable because the instant composition itself is patentable over Francois et al. either alone or in view of Becker et al, for the reasons given above.

Finally, applicants with full respect believe that the Examiner is indulging in hindsight analysis by stating that it would be obvious to combine the teachings of Francois et al. and Becker et al. Absent guidance in Francois et al. to consider, as an issue, <u>forming and maintaining a eutectic mixture</u> of at least first and second active agents in at least one discontinuous phase of an emulsion, there is nothing to motivate a person skilled in the art to combine the

disclosures of Francois et al. and Becker et al.

Applicants respectfully submit that there is simply nothing in either Francois et al. or Becker et al. that would have motivated one skilled in the art to combine these disclosures. Moreover, even if combined, there is clearly no suggestion of forming and maintaining a eutectic mixture of at least first and second active agents in at least one discontinuous phase of an emulsion. The Examiner's conclusion that one skilled in the art would use xanthan gum to form and maintain a eutectic mixture of at least first and second active agents in at least one discontinuous phase of an emulsion is clearly impermissible hindsight analysis since there is simply no suggestion in Francois et al. or Becker et al. to that effect. Accordingly, it is respectfully submitted that Claim 30 is also clearly patentable.

In conclusion, applicants submit that none of the cited art, whether taken alone or together, discloses or suggests forming and maintaining a eutectic mixture of at least first and second active agents in at least one discontinuous phase of an emulsion. Accordingly, applicants respectfully requests favorable reconsideration and early passage to issue of this application.

No fee, other than the enclosed $110.00 extension of time fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

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